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Influence of menopausal status on postprandial lipoprotein metabolism

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Introduction

Menopausal status is a significant determinant of coronary heart disease (CHD) risk. A more pro-atherogenic lipoprotein profile mediated by an increase in circulating triglyceride (TAG) levels, is thought to be partly responsible for the increased risk in postmenopausal women. In addition to the ability of TAG-rich lipoproteins (TRL) to directly sequester lipids into the atheroma, elevated TRL is known to have a deleterious effect on the atherogenicity of other lipoprotein classes resulting in an increase in the percentage of low-density lipoprotein (LDL) as LDL-3 and a decrease in overall HDL-cholesterol levels. Although postprandial TAG is known to be a more significant determinant of CHD risk relative to fasting levels, detailed information on the effect of menopausal status on postprandial lipoprotein metabolism is lacking.

Methods

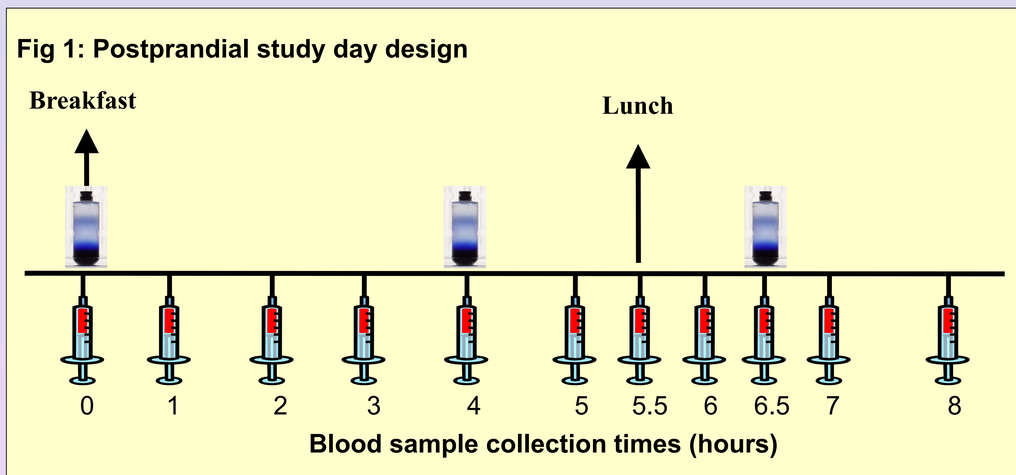
Postprandial assessment and plasma lipoprotein separation

Postprandial assessment and plasma lipoprotein separation was carried out on 22 healthy female volunteers (premenopausal n=12, postmenopausal n=10). The volunteers were between the ages of 25-70 years with a body mass index (BMI) 20-32 kg/m², plasma TAG 0.5-3.0 mmol/L, plasma total cholesterol (TC) 5.0-8.0 mmol/L, glucose <6.8 mmol/L, haemoglobin >11g/dl and blood pressure <160/95 mmHg. Postmenopausal status was defined as not having menstruated in the previous 2 years.

Study design

For 24 hours prior to the postprandial assessment the volunteers refrained from strenuous exercise and alcohol. On arrival at the Nutrition Unit at 8am in a 12h fasted state, weight, height and blood pressure were recorded, and an in-dwelling cannula inserted into the antecubital vein of the forearm. Following a standard breakfast (t=0h, 49g fat; 19g protein; 111g carbohydrate) and lunch (t=5.5h, 29.g fat; 15g protein; 63g carbohydrate) regular blood samples ( ) were collected into EDTA tubes up to 8h post-breakfast (Fig 1).

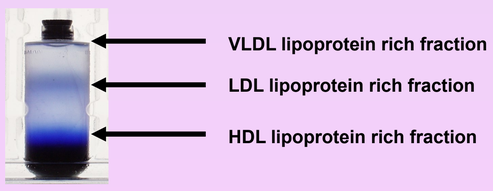
Fig 1: Postprandial study day design



Blood sample processing and lipoprotein separation

Plasma sample was isolated by centrifugation at 3000rpm for 15mins. At fixed time points (0, 4 and 6.5h) the chylomicrons were separated from the plasma (10000rpm, 30min) and further lipoprotein (VLDL, LDL, HDL) isolation carried out using the iodixanol method ( ) (65000rpm, 190min)(2). See Fig 2 below.

Fig 2: Lipoprotein bands in optiseal tube after ultracentrifugation with iodixanol



Analysis of plasma samples and lipoprotein fractions

Plasma TC, TAG, HDL-C, glucose and lipoprotein TAG and apoB concentrations were measured using commercially available kits (Instrumentation Laboratory, Warrington, UK) on the ILab™ 600 Clinical Chemistry System (Instrumentation Laboratory).

Statistical analysis

Results are expressed as group means ± SEM. Differences between groups were assessed using t-tests and Mann-Whitney U tests for parametric and non-parametric data respectively. A $P < 0.05$ was taken as significant.

References

1. Graham et al. A novel method for the rapid separation of plasma lipoproteins using self-generating gradients of iodixanol. *Atherosclerosis*. 1996;124:125-135.
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Results

Comparison of pre- and postmenopausal women at baseline (t=0h) (Table 1) indicated significantly higher TC, LDL-C, apoB and glucose in the postmenopausal group (P<0.05). The trends towards lower HDL-C and higher fasting TAG levels in this group failed to reach significance.

Table 1: Baseline characteristics of the study participants. Values are mean ± SEM.

Variables	All (n=22)	Premenopausal (n=12)	Postmenopausal (n=10)	P*
Age (y)	49 ± 3	40 ± 2	60 ± 2	0.000
Body mass index (kg/m²)	23.9 ± 0.6	23.0 ± 0.5	24.9 ± 1.1	0.146
TC (mmol/L)	5.27 ± 0.21	4.71 ± 0.19	5.94 ± 0.28	0.001
TAG (mmol/L)	1.10 ± 0.05	1.00 ± 0.08	1.22 ± 0.06	0.193
HDL-C (mmol/L)	1.66 ± 0.07	1.70 ± 0.10	1.62 ± 0.11	0.599
LDL-C (mmol/L)	3.12 ± 0.21	2.51 ± 0.20	3.84 ± 0.24	0.000
Glucose (mmol/L)	4.78 ± 0.08	4.59 ± 0.10	5.00 ± 0.11	0.011
ApoB (ug/ml)	814.6 ± 38.9	738.5 ± 41.0	905.8 ± 60.3	0.035
Systolic BP (mmHg)	120 ± 4	116 ± 3	125 ± 7	0.255
Diastolic BP (mmHg)	72 ± 1	71 ± 1	73 ± 3	0.673

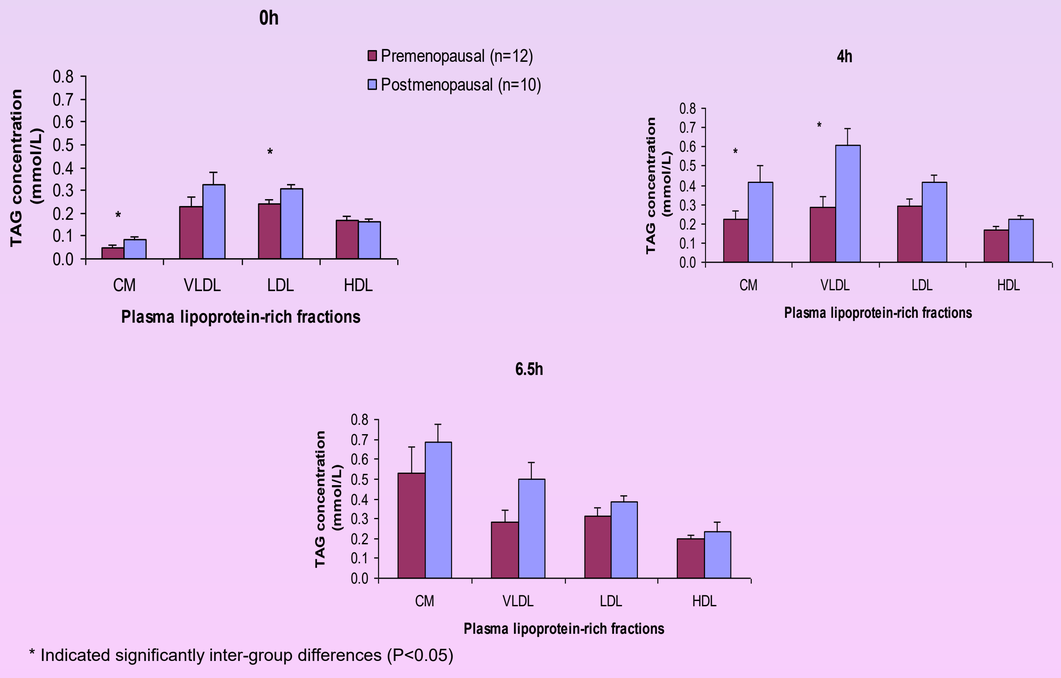
TC-total cholesterol; TAG-triglyceride; HDL-C-high density lipoprotein cholesterol; LDL-C- low density lipoprotein cholesterol; BP-blood pressure; Hb haemoglobin; AUC-area under the curve; IAUC-incremental area under the curve. LDL-cholesterol (LDL-C) was determined using the Friedewald formula (2) and area under the postprandial curve (AUC) and incremental AUC (IAUC) calculated using the trapeziodal rule.

Thirty one percent (31%) and 54% higher TAG AUC and IAUC were evident in the postmenopausal group (Fig 3). However the intergroup differences failed to reach significance (P= 0.056 and 0.092). At t=6h premenopausal women have significantly lower TAG levels (P=0.027) than postmenopausal women.

Fig 3: Average postprandial TAG response in group as a whole and according to menopausal status

Fig 4: Average postprandail TAG:apoB ratio in group as a whole and according to menopausal status

Fig 5: Average TAG concentration in the baseline and postprandial separated plasma lipoprotein fractions at 0, 4 and 6.5h



* Indicated significantly inter-group differences (P<0.05)

Analysis of the lipoprotein subfractions illustrates that the postmenopausal group have relatively more TAG within the lipoprotein-rich fractions (CM, VLDL, LDL and HDL) than the premenopausal group. At t= 0h, the mean CM-TAG and LDL-TAG are significantly higher (P=0.028 and 0.030) and at t=4h CM-TAG and VLDL-TAG are significantly higher (P=0.044 and 0.030) in the postmenopausal group. Comparison between the timepoints shows a postprandial rise within the CM-rich and VLDL-rich lipoprotien fractions in both menopausal groups.

Discussion

In summary, the present data indicates a strong trend towards higher TAG content postprandially and delayed postprandial TAG-rich lipoprotein clearance within the postmenopausal group. However greater group numbers are needed within this study to take into account the high variability observed in TAG measurements. This initial data supports the view that postprandial TAG accumulation is likely to make a significant contribution to the increased CHD risk in postmenopausal women.